SYNOPSIS

Title	Estimation of the Energy Barrier for Micelle-mediated Nucleation Growth on Surfaces: Strategic Reduction and Application in Drug Delivery
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We investigated the nucleation and growth of gold nanocrystals on a gold surface influenced by CTAB micelles. Using molecular dynamics simulations, we explored how CTAB micelle acts as a template for gold nucleation, with surfactant molecules adsorbing onto the surface to stabilize and control the size and distribution of gold nanocrystals. To control the release of the engulfed nucleate into the micelle onto the substrate, one needs to understand its release mechanism and quantify the energy requirement for the process. Here, we have used an enhanced sampling technique (umbrella sampling, followed by weighted histogram analysis method) to calculate the free energy required for the above-mentioned process. An energy barrier of 10.36 ± 0.3 kcal/mol to break the strong layering of micelle and water on the substrate was estimated. The molecular arrangement from the biased simulations showed that spreading the micelles on the surface is essential for the process. Oleylamine (OLA), a co-surfactant with CTAB, formed cylindrical micelles and was introduced to reduce this barrier. This approach aims to lower the energy barrier and enhance nucleate release efficiency.

The Co-surfactant, oleylamine (OLA), alters the micelle shape from spherical to cylindrical, facilitating confined nanocrystal growth. OLA also acts as a stabilizer, preventing nanocrystal aggregation and ensuring controlled particle size during synthesis. The co-surfactant OLA reduced the energy barrier to 8.42 ± 0.3 kcal/mol, which was instrumental in reducing these challenges, enabling effective nucleate release and adsorption. The strong affinity between the alkyl thiols and gold atoms was utilized to further engineer the micelle's behaviour. The addition of co-surfactant, Hexadecane Thiol (HT), significantly reduced the energy barrier for nucleate release to 2.83 ± 0.12 kcal/mol. However, despite these improvements, an energy barrier persists, largely due to hydration layers and micelle reorganization requirements. Reducing this energy barrier is crucial for optimizing nucleation and growth processes.

In order to break the strong layering of the water molecules on the surface, we introduced sparingly dispersed thiol molecules on the gold surface. The potential of mean force (PMF) displayed a persistent decrease in the energy towards the surface, and negative free energy change demonstrated that thiol-functionalized surfaces promoted the growth of the nucleate on the surface. Moreover, increasing thiol surface density further minimized the energy barrier due to enhanced hydrophobic interactions. The introduction of the hexadecane thiol layer significantly increases the energy barrier compared to an unfunctionalized surface, demonstrating the importance of steric and hydrophobic effects in modulating interaction forces. These findings provide valuable insights into the molecular-level mechanisms governing nanoparticle-surface interactions and offer guidelines for designing functionalized surfaces to optimize nanomaterial synthesis and surface engineering. The thiol layer reduces the energy barrier; the optimum surface density is 3.34×10^{-6} mol/m^2. This behaviour highlights the importance of optimizing the thiol surface density to balance stability and efficiency during nanoparticle synthesis. Overall, the results underscore the critical role of surface functionalization in promoting thermodynamic favorability and facilitating micelle-mediated nucleation processes.

We extended our study to the reverse process of drug release from chitosan-based matrices. In this study, we investigated the potential of chitosan-based membranes as a carrier for the controlled release of methotrexate (MTX), a widely used drug in cancer treatment.

The chitosan (CS) chains were cross-linked with sodium tripolyphosphate (STPP) to form a rigid matrix capable of encapsulating MTX. Molecular dynamics simulations were employed to assess the performance of the CS-based membranes in releasing MTX upon exposure to water. Encapsulating methotrexate (MTX) in a chitosan-stabilized system revealed an energy barrier of 81.1±0.81 kcal/mol for release in aqueous solution. We have calculated the potential of mean force to understand the energy landscape in the aqueous medium or ethanol-water solution. We have observed that the free energy in the ethanol-water solution reduced to 52.4±1.83 kcal/mol, as compared to an aqueous solution, further reduced to 5.33±1.77 kcal/mol after replacing cross-linker STPP with Chloride ions. In addition, we have shown the effect of the concentration of STPP on the binding of CS with MTX. Understanding how STPP concentration affects MTX release is crucial for designing drug delivery systems. By adjusting the concentration of STPP, one can fine-tune the release profile of the drug. We have also shown the comparative study of energy requirement to release a drug molecule from the CS matrix with and without STPP molecules. The pair correlation displayed that the water molecules have a stronger interaction with the STPP molecules compared to CS chains and MTX molecules. Our findings indicate that the CS nanoparticles exhibit promising characteristics for controlled drug release, making them a potential candidate for improving the efficacy and safety of MTX therapy in cancer treatment.

This study provided critical insights into the role of micelles and co-surfactants in nanocrystal nucleation, growth, and drug release mechanisms through molecular dynamics simulations. Cylindrical micelles formed by OLA and CTAB demonstrated the stability, adaptability, and facilitated gold nucleate aggregation. Introducing thiol-functionalized surfaces significantly reduced the energy barrier for nucleate incorporation, with higher thiol densities enhancing stabilization via hydrophobic interactions. For drug release, the chitosan-MTX system exhibited a high energy barrier, which was reduced with ethanol as a co-solvent, underscoring the influence of solvent composition and cross-linkers. These findings provide a comprehensive framework for optimizing nanomaterial synthesis and drug delivery systems.

ABSTRACT

Poly elemental nanoparticles (PENPs) offer multi-functionality with exceptional properties such as high mechanical strength, thermal stability, and fatigue resistance, but their synthesis is energy-intensive and challenging. A solution-based approach using micelles (CTABs) mediated nucleation and growth is investigated to address this. The free energy of gold nucleation to be grown on a gold surface within a spherical micelle is estimated using the Umbrella Sampling method. An energy barrier of 10.36±0.3 kcal/mol inhibited the nucleate-engulfed micelles from delivering the nucleate to the surface. Structural analysis showed that the spreading of micelle is essential to the discharge of engulfed nucleate. Adding a co-surfactant, oleylamine (OLA), with the primary surfactant, CTAB, formed a stable cylindrical micelle in water, which could reduce the energy barrier for the abovementioned purpose. The energy barrier decreases to 8.42±0.3 kcal/mol in this case. Micelle deformation, influenced by OLA, facilitates nucleate release onto the surface, followed by an energy increase due to nucleate-surface interactions. However, a significant energy barrier persists despite these improvements, mainly due to hydration layers and micelle reorganization requirements. Reducing this energy barrier is crucial for optimizing nucleation and growth processes. The strong affinity between alkyl thiols and gold atoms was utilized to engineer the micelle's behaviour further. Hexadecane thiol molecules were infused into the micelle, and a subsequent reduction in the energy barrier was obtained (2.83±0.12 kcal/mol). To make the process spontaneous, the energy barrier, due to strong water layering, has to be removed. A sparingly dispersed monolayer of thiols was introduced on the targeted surface. The decrease in the potential of mean force (PMF) and negative free energy changes demonstrated that thiol-functionalized surfaces can make the process spontaneous. The surface density of thiols was further varied to

optimize the energy barrier, and found that 3.34×10^{-6} mol/m^2 was the optimum density. Finally, we extended our study to the reverse drug release process from chitosan-based matrices. Encapsulating methotrexate (MTX) in a chitosan-stabilized system revealed an energy barrier of 81.1±0.81 kcal/mol for release, which reduced to 52.4±1.83 kcal/mol upon adding ethanol as a co-solvent. Further, it decreased to 5.33±1.77 kcal/mol after replacing cross-linker STPP with Chloride ions. This highlighted the significant impact of solvent composition and cross-linkers like STPP on drug encapsulation and release.